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nature REVIEWS Story by Rachel Smallridge, *Nature Reviews Molecular Cell Biology*

A small fortune

The world of small RNAs just got bigger. In *Caenorhabditis elegans* , two small temporal RNAs produced by the ribonuclease Dicer have previously been shown to be involved in regulating developmental timing. These RNAs lin-4 and let-7, 22 and 21 nucleotides in length, respectively act as antisense repressors of messenger RNA translation and, until recently, they were the only known RNAs of this class. But three papers published in *Science* now show that *lin-4* and *let-7* probably belong to a large family of single-stranded RNAs, 20—24 nucleotides in length, called microRNAs (miRNAs). These results indicate that post-transcriptional regulation by small RNAs is more common than previously believed.

Lagos-Quintana and colleagues used complementary DNA libraries constructed from a size-fractionated RNA population to identify 14 new miRNAs in *Drosophila melanogaster* and 19 new miRNAs in humans. Lau *et al* . created a cDNA library enriched for Dicer products, distinguished from other oligonucleotides by their small size, 5'-monophosphate group and 3'-hydroxyl group, to identify 54 novel miRNAs in *C. elegans* . Finally, using size-selected cDNA cloning together with computational methods, Lee and Ambros identified 15 miRNAs in *C. elegans* , 11 of which matched those identified by Lau and co-workers. In all cases, they showed the miRNAs were not simply the breakdown products of mRNAs or structural RNAs.

These papers identified 91 different miRNAs in total, about 12% of which have been conserved through evolution. Moreover, Lau and colleagues found that ~85% of the miRNAs identified in *C. elegans* had homologues in the 90%-complete *C. briggsae* genome sequence.

miRNAs are produced through processing probably by Dicer of a ~70-nucleotide precursor stem—loop structure. Either the 5' or the 3' arm of the precursor can be released to form the miRNA, with one exception. miR-56, identified by Lau *et al* ., exists in two forms, resulting from processing of both the 5' and 3' arms of the precursor stem. How miRNA excision occurs has yet to be defined.

The *mir* genes often cluster together in the genome; for example, Lagos-Quintana and colleagues showed that *mir-3* , *-4* , *-5* and *-6* form a gene cluster in the *Drosophila* genome. The *mir* gene clusters investigated so far are co-expressed, and Lau and co-workers predicted that, in *C. elegans* , the gene cluster *mir-35* to *-41* is transcribed to form a single RNA precursor, which is processed to produce miR-35 to -41. Some *mir* genes have multiple genomic copies, and some miRNAs are highly homologous.

All three groups investigated the expression of miRNAs and found that, in some cases, it was both stage- and tissue-specific. For example, Lee and Ambros found that *mir-1* is expressed stage-specifically in mouse embryogenesis and tissue-specifically in the human heart. These regulated expression patterns indicate an involvement in developmental control.

miRNAs have been proposed to function as 'riboregulators', regulating gene expression by binding sequence-specifically to mRNAs, thereby blocking translation. The challenge now is to define the potential targets of miRNAs and their exact functions. There are probably many miRNAs yet to be identified and, if they are found to be as numerous and diverse as the miRNAs identified in these papers, they could have a range of regulatory functions. These authors seem to have discovered a small fortune, and the world of small RNAs could turn out to be very big indeed.

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1: Science 2001 Oct 26;294(5543):853-8

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Identification of Novel Genes Coding for Small Expressed RNAs.

Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T.

Department of Cellular Biochemistry, Max Planck Institute for Biophysical Chemistry, Am Fassberg 11, D-37077 Gottingen, Germany.

In Caenorhabditis elegans, lin-4 and let-7 encode 22- and 21-nucleotide (nt) RNAs, respectively, which function as key regulators of developmental timing. Because the appearance of these short RNAs is regulated during development, they are also referred to as small temporal RNAs (stRNAs). We show that many 21- and 22-nt expressed RNAs, termed microRNAs, exist in invertebrates and vertebrates and that some of these novel RNAs, similar to let-7 stRNA, are highly conserved. This suggests that sequence-specific, posttranscriptional regulatory mechanisms mediated by small RNAs are more general than previously appreciated.

PMID: 11679670 [PubMed - in process]

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Riddle, Donald L.; Blumenthal, Thomas; Meyer, Barbara J.; Priess, James R., editors.
Plainview (NY): Cold Spring Harbor Laboratory Press; c1997.

22 items in **Molecular Biology of the Cell.** 3rd ed.
Alberts, Bruce; Bray, Dennis; Lewis, Julian; Raff, Martin; Roberts, Keith; Watson, James D.
New York and London: Garland Publishing; c1994

4 items in **Introduction to Genetic Analysis.** 7th ed.
Griffiths, Anthony J.F.; Gelbart, William M.; Miller, Jeffrey H.; Lewontin, Richard C.
New York: W H Freeman & Co; c1999.

22 items in **Molecular Cell Biology.** 4th ed.
Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E.
New York: W H Freeman & Co; c2000.

2 items in **Modern Genetic Analysis.**
Griffiths, Anthony J.F.; Gelbart, William M.; Miller, Jeffrey H.; Lewontin, Richard C.
New York: W H Freeman & Co; c1999.

27 items in **Retroviruses.**
Coffin, John M.; Hughes, Stephen H.; Varmus, Harold E.
Plainview (NY): Cold Spring Harbor Laboratory Press; c1997.

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